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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Stefan Russwurm

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EXAMINER

KAPUSHOC, STEPHEN THOMAS

ART UNIT

PAPER NUMBER

1634

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 0/551,874	Applicant(s) RUSSWURM ET AL.
	Examiner STEPHEN KAPUSHOC	Art Unit 1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 May 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10,12-37,39-56,60 and 61 is/are pending in the application.
- 4a) Of the above claim(s) 1,3,8,12,14,20,21,30-37,39-56 and 60 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2, 4-7, 9, 10, 13, 15-19, 22-29 and 61 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>6/12/11;2/24/11;4/2/10;2/26/10</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-10, 12-37, 39-56, 60 and 61 are pending.

Claims 1, 3, 8, 12, 14, 20, 21, 30-37, 39-56, and 60 are withdrawn from examination as detailed in the previous Office Actions of 03/05/2009 and 11/24/2009.

Claims 2, 4-7, 9, 10, 13, 15-19, 22-29 and 61 are examined on the merits.

It is noted that Applicants have indicated that claim 61 is withdrawn from examination (p.15 of Remarks of 05/25/2010). However, this claim encompasses the elected combination of sequences (see p.12-15 of the Election of 11/20/2008). As such the claim, is no far as it requires the elected combination, is examined on the merits.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/25/2010 has been entered.

This Office Action is in reply to Applicants' correspondence of 05/25/2010.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is **NON-FINAL**.

Please Note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

1. Applicant's remarks in continued traversal of the restriction requirement and the alleged unity of invention of different claimed methods (p.15-18 of the Remarks of 05/25/2010) have been fully and carefully considered but are not found to be persuasive. Applicants have argued that while the Examiner asserts that the common technical feature of the independent claims (using RNA levels to diagnose pathology) is taught in the prior art of Anderson (see p.2 of the Office Action of 11/24/2009), the instant specification teaches examples wherein SIRS, sepsis, or severe sepsis is diagnosed by comparing RNA levels different from normal levels, whereas Anderson teaches monitoring levels in an individual over time to make a diagnosis. Initially it is noted that this argument is not found to be persuasive because there is no limitation in the claims as to the source of any control (e.g.: the subject individual at an earlier time point; a separate control population). It is also noted, the instant specification in fact appears to exemplify a methods as is taught by Anderson (e.g.: p18 of the instant specification), where RNA samples are analyzed in individuals prior to a surgical procedure, and then RNA samples are analyzed in the same subjects at a different time point after a procedure.

Furthermore, after a review of the requirements of the claims and the teachings of the specification, it is noted that the claims methods of the claims have different structural requirements for operation. That is the methods for detecting SIRS (claim 1), the methods for detecting sepsis (claim 2), and the methods for detecting severe sepsis (claim 3) require the analysis of different genes for diagnosis. Page 10 of the specification, paragraphs 39, 40 and 41 disclose that there are in fact separate genes

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that are required for analysis and diagnosis of the different phenotypes. As such, the different methods require distinct analytes that do not share any substantial common structural features that are related to a common functional property.

The lack of unity restriction requirement is still deemed to be appropriate and is **MAINTAINED.**

***Maintained Claim Objections
Newly Applied to Claim 13***

2. Claims 13 and 61 are objected to for the specific recitation of non-elected subject matter. Applicants have elected for the specific combination of genes with the sequences as set forth in the first 57 sequences identified in the Table on pages 13-14 of the Remarks of 11/20/2008. Claim 61 encompasses any combination of 'SEQUENCE ID No. I.1 to SEQUENCE ID No. I.6242', and claim 13 encompasses any combination of the recited genes which includes (the last five genes listed in the table of claims 13) non-elected sequences; thus each claim encompasses numerous combinations and subcombinations of sequences different than the specific elected combination. It is noted that no claim is allowed in this Office Action. Upon allowance of a claim directed to the elected invention, the Examiner will consider rejoinder of the subject matter of the non-elected combinations, and rejoinder of any combinations that include all of the limitations of the allowed elected subcombination. Prior to allowance, any non-elected subject matter that is not re-joined with the elected subject matter will be required to be removed from the claims.

Withdrawn Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

3. The rejection of claims 26-29 under 35 U.S.C. 112, second paragraph, as set forth on pages 4-5 of the Office Action of 11/24/2009, are **WITHDRAWN** in light of the amendments to the claims.

Maintained Claim Rejections - 35 USC § 112 1st ¶ - Written Description

4. Claims 2, 4-7, 9, 10, 15-19 and 22-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants may wish to consult the Written Description Training Materials revised March 25, 2008, available online at www.uspto.gov/web/menu/written.pdf.

The rejection of claims for lack of adequate written description is relevant to the rejected claims, drawn to methods for in vitro diagnosis of sepsis and/or sepsis-like condition, as they require gene markers that are 'specific for sepsis and/or sepsis-like systemic inflammatory conditions or sepsis-like systemic infections' (as recited for example in independent claim 2). In the instant case the specification does not provide the skilled artisan with written description that adequately identifies characteristics of particular nucleic acids suitable for performing the claimed method as generically encompassed by the claims (i.e. the claims generically require nucleic acids with the

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functionality of being 'specific for sepsis and/or sepsis-like systemic inflammatory conditions or sepsis-like systemic infections'.

Relevant to the lack of particular structural limitations in the rejected claims,

MPEP 2163 states:

The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art.

In the instant case, genes as generically encompassed by the claims wherein the expression is diagnostically indicative of specific for sepsis and/or sepsis-like systemic inflammatory conditions or sepsis-like systemic infections are not known in the prior art (as generically recited in the claims, encompassing any genes or gene fragments from the human genome). Further, while the specification asserts that there is a group of genes from humans that are differentially expressed in humans with sepsis as compared to a non-septic individual (i.e. Tables 8 and 9), there is no disclosed relationship between the structure of the genes (i.e. their nucleotide sequences) and their functionality (i.e. diagnostic of sepsis) such that the skilled artisan would recognize that Applicants are in possession of the methods as generically claimed which encompass the use of any gene or fragment thereof.

In conclusion, having considered the breadth of the claims, and the particular teachings of the instant specification, and the teachings of the prior art, the specification, while providing a written description of methods requiring the step of, for example:

Comparing the abundance of particular mRNA species from a sample to the abundance of the same mRNA species from a control sample, wherein the mRNA

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species comprise SEQ ID NOs: 220, 303, 529, 754, 844, 1705, 2370, 2449, 2468, 2481, 2709, 2831, 2928, 2948, 3068, 3079, 3209, 3268, 3305, 3317, 3331, 3399, 3424, 3433, 3482, 3508, 3523, 3624, 3676, 3765, 3796, 3873, 3879, 3881, 3917, 4060, 4096, 4122, 4141, 4268, 4328, 4450, 4528, 4609, 4654, 4695, 4705, 4937, 5265, 5338, 5418, 5542, 5567, 5647, 5779, 6018 and 6200

does not provide an adequate written description of the broadly claimed subject matter.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ for lack of an adequate written description. Applicants' arguments (p.19-24 of Remarks of 05/25/2010) have been fully and carefully considered but are not found to be persuasive to withdraw the rejection.

Initially it is noted that the rejection has been withdrawn in so far as it had been previously applied to claims 13 and 61.

Applicants have argued (p.20 and 21 of Remarks) that there is no functional requirement for any of the RNA or DNA fragments as generically recited in the claims. This is not persuasive, as the claimed methods are methods for diagnosing sepsis, and the claims in fact recite that the markers are 'specific for sepsis and/or sepsis-like systemic inflammatory conditions or sepsis-like systemic infections'. The claims are not drawn to a mere analysis by hybridization, but require that the results of a hybridization assay are diagnostically indicative of a specific phenotype. As such the Examiner maintains that the claims have generic breadth and also require a very specific functionality of the recited nucleic acids, where the functionality over the breadth of the encompassed RNA and DNA structures is not supported by the teachings of the specification. And while Applicants argue that (p.22 of Remarks) the specification

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teaches numerous examples of genes identified in sepsis development, the Examiner maintains that the disclosure of several specific genes (e.g.: hundreds of genes) does not support the generic breadth of the claims which encompasses any of the tens of thousands of genes present in the human genome. In the instant case the claims are not drawn to methods for determining whether or not a gene is associated with sepsis; the claims are drawn to diagnostic methods where gene expression is measured and compared and then sepsis is diagnosed. As such the Examiner maintains that the artisan practicing the method must have knowledge of what genes are suitable for use in the claimed diagnostic method, where the specification does not support the enormous breadth of the claims as they encompass any genes in the human genome.

The rejection as set forth is **MAINTAINED**.

Maintained Claim Rejections - 35 USC § 112 1st ¶ - Enablement

5. Claims 2, 4-7, 9, 10, 13, 15-19, 22-29 and 61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and breadth of the claims

The claims are drawn to methods of diagnosis of sepsis and/or sepsis like conditions in human.

The claims generically encompass analysis of any gene or fragment specific for sepsis.

The claims encompass any comparison of any labeled RNA, as well as any fragments of the elected combination of SEQ ID NOs.

The claims encompass detection of any condition that can be considered a 'sepsis-like condition'.

The claims thus require knowledge of a correlative association between any expression levels of a wide variety of RNA combinations and a variety of different phenotypes in different subjects.

Direction provided by the specification and working example

Relevant to the Election, the instant specification provides a comparative analysis (Example 3 – p.26) of gene expression in two human individuals, one classified as a sepsis patient and the other classified as a non-septic control subject (Table 7). The specification provides asserts that 54 particular genes were overexpressed in the sepsis-patient sample (Table 8), and 56 particular genes were under-expressed in the sepsis-patient sample (Table 9).

Relevant to the claims and the elected invention, the specification provides the aforementioned analysis of sepsis gene expression, but does not provide for gene expression in the generic 'sepsis-like conditions'.

The specification provides only the results of a comparison between two individual subjects (a single case and a single control), with no validation of the asserted particular mRNAs specific for sepsis, nor any analyses of populations of cases or

controls. There is no statistical analysis of the reliability of classification using expression of particular mRNA species.

Additionally it is noted that the particular mRNAs asserted in the specification (Tables 8 and 9) to be indicative of sepsis are not included in the particular mRNAs of the Election.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to determining the abundance of any particular nucleic acid biomarker or combination of biomarkers is high, the unpredictability associated with correlating any comparison of abundances with a particular phenotype such as sepsis, is even higher. Such unpredictability is demonstrated by the prior art, the post-filing art, and the instant specification.

Because the claims encompass comparing any abundances of any particular RNAs to any control RNAs, where the specification provides only the example of analysis of two individuals (one case and one control), it is relevant to point out the unpredictability in using gene expression to establish a phenotype. For example, Cheung et al (2003) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). Additionally, the

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prior art of Shalon et al (2001) teaches that preferably 20-50 different test individuals are assayed to obtain meaningful data showing a significant change in gene expression levels, and changes of gene expression of at least 2 fold and up to 100 fold or more are desirable for the comparison of gene expression levels between a case and control population (p.10 ¶156, ¶158). Further, it is known in the art that the p-value of any marker used to diagnose sepsis will change based on the size of the population used for comparison (PG Pub US 2004/0106142, p.14, ¶[0127]).

Given the lack of any statistical significance in the methods, it is relevant to point out that the prior art of Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant (Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of 0.05 would not be considered strong enough for the basis of a conclusion).

Because claims encompass the analysis of gene expression in any body fluid, whereas the specification provides only expression in whole blood samples, it is relevant to point out the unpredictability in comparing gene expression among different tissues. Cobb et al (2002) teaches the unpredictability in analysis of gene expression different tissue sample types of a septic mammal, specifically in spleen and liver samples from septic mice. Notably, the reference teaches that, when compared to a non-septic sample, the relevant expression profiles of the septic mouse spleen and the

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septic mouse liver contain different nucleic acids at different levels (Table 1; p.2714, middle col., Ins.2-8).

Quantity of experimentation required

A large and prohibitive amount of experimentation would be required to make and use the claimed invention. One would have to establish that any level of nucleic acid abundance of any RNAs (as generically encompassed by the claims), as compared to a control, is indicative of sepsis. Such experimentation would require case:control analysis of a population large enough to attain statistical significance, and require the analysis of different tissue types and analysis of any RNA species of interest. Even for the particularly elected SEQ ID NOs it is noted that the instant specification does not provide that these mRNAs are robustly and reliably diagnostic of the presence of sepsis or any other condition that may be considered 'sepsis-like', as encompassed by the claims, and may be used in a method of sepsis diagnosis.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the particular examples, it is the conclusion that an undue amount of experimentation would be required to make and use the claimed invention.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ for lack of enablement. Applicants' arguments (p.25-33 of Remarks) have been fully and carefully considered but are not found to be persuasive to withdraw the rejection.

Applicants have argued (p.29) that disclosure teaches RNA levels that are indicative of sepsis, and that this association is the invention, and thus the specification is enabled for the generic breadth of the claims as encompassing any RNA. This argument does not address the great unpredictability in gene expression studies as detailed by the Examiner in the rejection. The Examiner maintains that because of the lack of significance of the study in the specification which exemplifies the analysis of one case and one control subject, with no validation of the specifically disclosed genes, there is in fact no reliable established connection between the specifically disclosed genes and the required diagnosis, and the specific exemplification does not enable the claims as they encompass any gene in the human genome.

The Applicants offer the circular argument (p.29-30) that the claim requires gene fragments that are specific for sepsis, "thus, the test per se is specific". However, this statement does not establish enablement of the claimed method of diagnosis, it merely invites the skilled artisan to perform a large amount of experimentation in hopes of finding genes the expression of which is diagnostic of sepsis, thus allowing the skilled artisan identify the genes 'specific for sepsis' and then be able to practice the claimed methods.

Applicants have additionally argued (p.31) that the claimed methods are not limited to blood, but this argument does not address the unpredictability associated with

gene expression in different fluids (as encompassed by the claims), nor the fact that the specification discloses only the analysis of blood samples.

The rejection as set forth is **MAINTAINED**.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 24-7, 9,, 10, 15-19 and 22-29provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 8 and 11-25 of copending Application No. 10/591,371 (US PG Pub 2008/0286763). Although the conflicting claims are not identical, they are not patentably distinct from each other because the rejected claims and the conflicting claims are both drawn to methods for using RNA expression in a sample, as compared to a control, to determine a diagnosis of sepsis.

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This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

8. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days.

Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Stephen Kapushoc/
Primary Examiner, Art Unit 1634